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<p>(54) Title: COMPOSITIONS AND METHODS EMPLOYING R(-) FLUOXETINE AND OTHER ACTIVE INGREDIENTS</p> <p>(57) Abstract</p> <p>Pharmaceutical compositions which comprise R(-) fluoxetine and one or more other biologically active compounds are disclosed. Methods of treating or preventing a disease or disorder, especially a psychotic or psychiatric disease or disorder, using the above pharmaceutical composition or by administering a R(-) fluoxetine in combination with one or more other biologically active compounds are also disclosed. Methods of treating patients having or at risk of having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression and post-traumatic stress disorder using optically pure R(-) fluoxetine in combination with one or more other biologically active compounds are further disclosed.</p>		

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COMPOSITIONS AND METHODS EMPLOYING R(-)
FLUOXETINE AND OTHER ACTIVE INGREDIENTS

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1. FIELD OF THE INVENTION

This invention relates to pharmaceutical compositions and methods of treatment or prevention employing two or more active ingredients.

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2. INTRODUCTION

The present invention encompasses pharmaceutical compositions which comprise, and methods which utilize, optically pure R(-) fluoxetine and a second biologically active compound, preferably, a benzodiazepine compound, a tricyclic antidepressant, a 5-HT_{1A} receptor antagonist, a 5-HT₂ receptor agonist, a β -adrenergic antagonist, an antipsychotic agent, an anti-anxiolytic or other psychotropic drug. The present invention is well suitable for treating patients, having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression, posttraumatic stress disorder or psychiatric disorder.

3. BACKGROUND OF THE INVENTION

Fluoxetine, N-methyl-3-phenyl-3-[(α,α,α -trifluoro-p-tolyl)-oxy]-propylamine, is marketed as the hydrochloride salt form of the racemic mixture under the tradename PROZAC[®] (U.S. Patent 4,314,081). PROZAC[®] is indicated for the treatment of depression, obsessive-compulsive disorder (OCD) and bulimia nervosa (Physician's Desk Reference[®] 52 Edition 1998, pages 859-860).

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As disclosed in U.S. Patent No. 5,708,035, the racemic mixture of fluoxetine has certain disadvantages including headaches, nervousness, anxiety, insomnia, akathisia, severe anxiety leading to intense violent suicidal thoughts and self mutilation, manic behavior, nausea, diarrhea, drowsiness, decrease in libido, and/or sexual dysfunction. The major

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disadvantage of the racemic mixture of fluoxetine is its long half-life and long duration of action. This long half-life can lead to a buildup of fluoxetine in the patient's body and a concomitant increase in the above described side effects when a patient is given multiple doses. More importantly, its long half-life and long duration of action also makes it impossible or impractical to use the racemic mixture of fluoxetine as part of a combination therapy, although combination therapy might be very desirable.

R(-) fluoxetine, and its use, is described in U.S. Patent Nos. 5,708,035 and 5,648,396 to Young et al. These patents state that the use of R(-) fluoxetine decreases the incidence of adverse effects seen with the racemic mixture of fluoxetine. These patents also state that R(-) fluoxetine is useful in the treatment of depression, migraine headaches, pain, in particular chronic pain, psychoactive substance abuse disorders and obsessive compulsive disorders. Additionally, U.S. Patent No. 5,648,396 discloses a method of treating depression in a human by first administering R(-) fluoxetine followed by a subsequent administration of a monoamine oxidase inhibitor.

U.S. Patent No. 5,356,934 discloses a method for treating sleep apnea in mammals which comprises administering to mammal requiring sleep apnea treatment an effective amount of (R)-fluoxetine or a pharmaceutically acceptable acid addition salt or solvate thereof.

U.S. Patent No. 4,035,511 discloses a method of producing analgesia or reducing hyperalgesia by administering racemic fluoxetine either alone or with morphine sulfate.

U.S. Patent No. 4,329,356 discloses a method for lowering blood pressure in a hypertensive mammal which comprises the co-administration of racemic fluoxetine and 1-5-hydroxytryptophane, or preferably the co-administration of fluoxetine, 1-5-hydroxytryptophane and a peripheral decarboxylase inhibitor such as carbidopa [α -hydrazino- α -methyl- β -(3,4-dihydroxyphenyl)propionic acid monohydrate] or

banserazide [n-(dl-seryl)-n"-(2,3,4-trihydroxybenzyl)hydrazine].

U.S. Patent No. 4,594,358 and U.S. Patent No. 4,683,235
5 discloses, respectively, a method of potentiating
dextropropoxyphene or codeine analgesia in mammals, either
alone or in combination with aspirin or acetaminophen, which
comprises the administration of an effective amount of
racemic fluoxetine or norfluoxetine prior to, concomitantly
10 with, or after the administration of dextropropoxyphene or
codeine which, if given alone, would produce less than the
desired analgesic effect.

U.S. Patent No. 4,895,845 discloses a method of
assisting weight loss in patients through the concomitant
administration of a rauwolfia alkaloid and at least one
15 antidepressant selected from the group consisting of
aminoazoles, phenoxyphenylpropylamine antidepressants such as
fluoxetine, and aminopropiophenones, or preferably through
the concomitant administration of a rauwolfia alkaloid, at
least one antidepressant selected from the group consisting
20 of aminoazoles, phenoxyphenylpropylamines, and
aminopropiophenones, and one or more of the sympathomimetic
anorectic agents that have proved successful in some
instances in promoting patient compliance to a calorically-
restricted diet.

U.S. Patent No. 5,512,593 discloses a method of treating
depression comprising administering to a patient an opioid
antagonist selected from the group consisting of naltrexone,
naloxone and a compound selected from the group consisting of
30 one or more non-tricyclic antidepressants exhibiting
serotonin reuptake inhibition in the synapses of the central
nervous system such as bupropion, sertraline, fluoxetine, and
trazodone.

U.S. Patent No. 5,527,788 discloses the use of DHEA and
at least one anorectic agent, such as fenfluramine HCl,
35 phentermine HCl, phendimetrazine tartrate, mazindol,

diethylpropion HCl, and fluoxetine HCl, in combination to produce weight loss in animals.

U.S. Patent No. 5,532,268, U.S. Patent No. 5,538,992 and
5 U.S. Patent No. 5,552,429 discloses, respectively, a method
for potentiating the action of fluoxetine, in increasing the
availability of serotonin, norepinephrine and dopamine in the
brain, comprising administering fluoxetine to a patient in
need thereof in combination with a second component which is
10 chosen from the group consisting of alprenolol, WAY 100135,
spiperone, propranolol and tertatolol, pindolol, or a
compound of the formula I that is described therein.

WO 92/00103 discloses a pharmaceutical product
comprising two or three active ingredients selected from a 5-
15 HT₂ receptor antagonist, a 5-HT re-uptake inhibitor such as
fluoxetine and a 5-HT₁ receptor agonist, as a combined
preparation for simultaneous, separate or sequential use in
therapy of depression and/or migraine.

WO 96/09044 discloses compositions for the effective
20 treatment of a variety of chronic and intractable disorders,
such as intractable coughing, dermatitis, chronic pain and
tinnitus, which failed to respond to other treatments. The
compositions are a therapeutically effective dosage of
dextromethorphan (DM) in combination with a therapeutically
25 effective dosage of an inhibitor of enzymatic
dextromethorphan oxidation by the liver enzyme debrisoquin
hydroxylase. As disclosed therein, antioxidants include
yohimbine, fluoxetine, haloperidol, ajmaline, lobeline,
pipamperone.

WO 96/09047 discloses a method of treating alcoholism
30 and alcohol dependence in a mammal comprising administering
to the mammal a therapeutically effective amount of a
synergistic combination of at least one opioid antagonist,
and at least one selective serotonin reuptake inhibitor. The
phrase "selective serotonin reuptake inhibitor", as used
35 therein, denotes compounds which enhance brain serotonergic
activity by blocking the neuronal reuptake and subsequent

inactivation of serotonin at synaptic junctions between nerve cells; such include fluoxetine, sertraline, paroxetine, venlafaxine, fluvoxamine, nefazodone, citalopram, and zimeldine.

5 WO 97/31629 discloses a method of treating disorders of sleep comprising administering to a patient in need of such treatment a first component chosen from the group consisting of fluoxetine, venlafaxin, citalopram, fluvoxamine, 10 paroxetine, milnacipran and duloxetine in combination with a second component chosen from the group consisting of alprenolol, WAY 100135, WAY 100635, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula I as described therein.

15 From the above, it appears that the art has been exploring the use of racemic fluoxetine in combination with other drugs for a number of uses. However, there is a need for combination therapy with the advantages of racemic fluoxetine without the disadvantages of racemic fluoxetine such as the great potential for adverse drug-drug 20 interactions.

4. SUMMARY OF THE INVENTION

The present invention encompasses a pharmaceutical composition which comprises an effective amount of optically 25 pure R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of second biologically active compound and a pharmaceutically acceptable carrier. The present invention also relates to a method of treating or preventing diseases 30 or disorders in humans, especially a psychotic or psychiatric disease or disorder, using such pharmaceutical compositions.

The present invention also encompasses a method of treating or preventing a psychotic or psychiatric disease or disorder by administering optically pure R(-) fluoxetine and 35 a second biologically active compound, preferably a benzodiazepine compound, a tricyclic antidepressant, an

antipsychotic agent, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₂ receptor agonist, or a compound selected from the group consisting of lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium. The present invention further encompasses methods of treating patients, having or at risk of having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression, posttraumatic stress disorder or other psychiatric disorders, using optically pure R(-) fluoxetine in combination with one or more biologically active compounds.

Finally, the present invention encompasses methods of treating or preventing a psychotic or psychiatric disease or disorder which comprises administering an effective amount of R(-) fluoxetine and an amount of a biologically active 5-HT_{1A} receptor antagonist for a first period of time, and after the first period of time, administering an effective amount of R(-) fluoxetine and a reduced amount of said biologically active 5-HT_{1A} receptor antagonist for a second period of time; and kits to be used for such treatment or prevention.

Thus, the invention encompasses the use of R(-) fluoxetine, salts, solvates, hydrates and pro-drugs thereof in combination with one or more additional active ingredients. R(-) fluoxetine can be used in the same pharmaceutical composition as the one or more additional active ingredient, or R(-) fluoxetine can be administered concurrently or sequentially with the other active ingredients, i.e., before, during or after.

The present invention does not contemplate a pharmaceutical composition containing an effective amount of optically pure R(-) fluoxetine and an effective amount of a monoamine oxidase inhibitor. The present invention also does not encompass methods of treatment or prevention using optically pure R(-) fluoxetine in combination with a monoamine oxidase inhibitor.

Specific preferred combinations and further details of the invention are described in detail below.

5 5. THE DETAILED DESCRIPTION OF THE INVENTION

 The present invention encompasses pharmaceutical compositions which comprise a therapeutically effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of second biologically active compound, preferably, a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, a 5-HT_{1A} receptor antagonist such as pindolol, a 5-HT₂ receptor agonist, a β -adrenergic antagonist such as pindolol, an anti-anxiolytic, or a compound selected from the group consisting of lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium, and a pharmaceutically acceptable carrier.

 Any pharmaceutically acceptable salt of R(-) fluoxetine can be used in the present invention; however, acid addition salts are preferred. The most preferred pharmaceutically acceptable salt of R(-) fluoxetine is the hydrochloride salt.

 The compositions and methods of this invention employ the optically pure R(-) isomer of fluoxetine in combination with drugs that act on the central nervous system ("CNS"), such as 5-HT_{1A} receptor, including hypnotics and sedatives; drugs useful in treating psychiatric disorders, such drugs include antipsychotic or neuroleptic drugs, antianxiety drugs, antidepressants and mood-stabilizers; central nervous system stimulants such as amphetamines; dopamine receptor agonists; anticonvulsants; antipanic agents; and antipsychotic agents and the like. R(-) fluoxetine may also be used in combination with cardiovascular agents (beta blockers and ACE inhibitors); antivirals; antibiotics, antifungals; antineoplastics; and others.

 The present invention provides the skilled artisan with a substantial benefit, that is, the ability to use a SSRI

compound, such as R(-) fluoxetine, with one or more other active drugs without, or with reduced concern for, adverse drug-drug interactions. For example, R(-) fluoxetine can be used in a number of different patient populations including but not limited to cancer patients, cardiac patients, AIDS patients or HIV infected populations, and psychiatric patients, each of which is likely undergoing treatment with a drug other than racemic fluoxetine or is enantiomers. Further, many patients affiliated with life threatening diseases experience depression particularly at or about the time they first learned of their affliction. For example, victims of heart attacks are known to experience depression. Now these patients can be treated for their cardiac disorder as well as be treated for their depression while avoiding the adverse effects associated with the administration of racemic fluoxetine.

Moreover, the use of R(-) fluoxetine in combination with the drugs described herein provides an improved therapy over certain therapies presently available in the art; the use of R(-) fluoxetine and certain of the drugs may allow for treatment where none was previously available; and certain combinations can provide a synergistic benefit.

In a preferred embodiment, R(-) fluoxetine is used in combination with a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₂ receptor agonist, or one or more of the following compounds: lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium.

The preferred benzodiazepine compounds for use within the present invention include, but are not limited to, alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam or triazolam.

The preferred tricyclic antipsychotic compounds for use within the present invention include, but are not limited to, chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, 5 thiothixene, clozapine, haloperidol, loxapine, molindone, pimozide, risperidone or desipramine.

The preferred 5-HT_{1A} receptor antagonists for use within the present invention include, but are not limited to, 10 alprenolol, WAY 100135, spiperone, pindolol, (S)-UH-301, penbutolol, propranolol, tertatolol, and a compound of the formula I as disclosed in U.S. Patent No. 5,552,429, the content of which is herein incorporated by reference.

In a preferred embodiment, a pharmaceutical composition 15 of the invention comprises from about 5 mg to about 100 mg of R(-) fluoxetine, and the second biologically active compound, which is a benzodiazepine compound, a tricyclic antidepressant, an antipsychotic agent, an anti-anxiolytic, a β -adrenergic antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₂ 20 receptor agonist, or a compound selected from the group consisting of lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium. The dosage of the second biologically active compound can be easily determined by skilled artisans, e.g., following dosages recommended in the 25 Physician's Desk Reference® 52 Edition 1998.

In a preferred pharmaceutical composition, the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

The present invention also relates to a method of 30 treating or preventing a disease or disorder, especially a psychotic or psychiatric disease or disorder, using the above pharmaceutical composition.

The present invention further encompasses methods of treating or preventing a disease or disorder by administering 35 R(-) fluoxetine in combination with a second biologically active compound which is a benzodiazepine compound, a tricyclic antidepressant, an anti-anxiolytic, a β -adrenergic

antagonist, a 5-HT_{1A} receptor antagonist, a 5-HT₂ receptor agonist, or a compound selected from the group consisting of lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium.

5 The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a benzodiazepine include, but are not limited to, depression, anxiety, alcohol withdrawal, preoperative apprehension, Lennox-Gastaut syndrome (petit mal variant), bulimina nervosa, seizures, 10 bipolar disorders, panic disorder, skeletal muscle spasm, spasticity caused by upper motor neuron disorders, athetosis and stiffman syndrome, convulsive disorders and insomnia.

The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a tricyclic antipsychotic 15 compound include, but are not limited to, anxiety, depression, nausea, vomiting, restlessness and apprehension before surgery, acute intermittent porphyria, tetanus, intractable hiccups, severe behavioral problems and 20 hyperactivity in children, emotional withdrawal, conceptual disorganization, tension, hallucinatory behavior, suspiciousness and blunted affect in schizophrenic patients or Tourette's Disorder.

The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a 5-HT_{1A} receptor 25 antagonist include, but are not limited to, depression, obsessive-compulsive disorders, obesity and late luteal phase syndrome, hypertension, migraine, essential tremor, hypertrophic subaortic stenosis and pheochromocytoma. The 30 more preferred disease or disorder that can be treated or prevented using R(-) fluoxetine and a 5-HT_{1A} receptor antagonist includes, but is not limited to, posttraumatic depression disorder.

The diseases or disorders that can be treated or prevented using R(-) fluoxetine and a compound selected from 35 the group consisting of lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium include, but

are not limited to, anxiety, depression, hypertension and Attention Deficit Disorders.

5 The disease or disorder that can be treated or prevented using R(-) fluoxetine and a β -adrenergic antagonist includes, but is not limited to, post myocardial infarction depression. The preferred β -adrenergic antagonists include, but are not limited to, S(-) pindolol, penbutolol and propranolol.

10 As used in the present application, the terms "substantially free of the S(+) stereoisomer" and "optically pure R(-) fluoxetine" means that the composition contains at least 90% by weight of R(-) fluoxetine and 10% by weight or less of S(+) fluoxetine. In the most preferred embodiment the "substantially free of the S(+) stereoisomer" means that
15 the composition contains at least 99% by weight R(-) fluoxetine and 1% or less of S(+) fluoxetine.

Optically pure R(-) fluoxetine can be asymmetrically synthesized or it can be resolved using conventional techniques, both of which are known in the art. For example,
20 the synthesis of R(-) isomer of fluoxetine is disclosed in U.S. Patent Nos. 5,648,396 and 5,708,035, the contents of which are incorporated by reference.

Unless otherwise indicated herein, when the name of a chiral drug is used without modification that name refers to
25 the racemic mixture, the (+) and (-) isomers and mixtures thereof. For example, "pindolol" refers to racemic pindolol, S(+) pindolol, R(-) pindolol and mixtures of S(+) and R(-) pindolol.

The term benzodiazepine refers to the portion of the structure composed of a benzene ring (A) fused to a seven-
30 membered diazepine ring (B) (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 17, p 363). However, since all the important benzodiazepines contain a 5-aryl substituent (ring C) and a
35 1,4-diazepine ring, the term has come to mean the 5-aryl-1,4-benzodiazepines. Various modifications in the structure of

the ring systems have yielded compounds with similar activities.

The effects of the benzodiazepines virtually all result from actions of these drugs on the CNS. The most prominent of these effects are sedation, hypnosis, decreased anxiety, muscle relaxation, anterograde amnesia, and anticonvulsant activity. A variety of benzodiazepine-like effects have been observed *in vivo* and *in vitro* and have been classified as full agonistic effects (*i.e.*, faithfully mimicking agents such as diazepam with relatively low fractional occupancy of binding sites) or partial agonistic effects (*i.e.*, producing less intense maximal effects and/or requiring relatively high fractional occupancy compared to agents such as diazepam).

Examples of benzodiazepines that can be used in the present invention include, but are not limited to, alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 17, p363, Table 17-1).

XANAX® tablets contain alprazolam which is a triazolo analog of the 1,4 benzodiazepine class of central nervous system-active compounds (Physician's Desk Reference® 52 Edition 1998, page 2294). The chemical name of alprazolam is 8-Chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3- α][1,4]benzodiazepine. XANAX Tablets (alprazolam) are indicated for the management of anxiety disorder (a condition corresponding most closely to the APA Diagnostic and Statistical Manual [DSM-III-R] diagnosis of generalized anxiety disorder) or the short-term relief of symptoms of anxiety.

LIBRIUM® (chlordiazepoxide HCl) is 7-chloro-2-(methylamino)-5-phenyl-3H-1,4-benzodiazepine 4-oxide hydrochloride (Physician's Desk Reference® 52 Edition 1998,

page 2522). Librium is indicated for the management of anxiety disorders or for the short-term relief of symptoms of anxiety, withdrawal symptoms of acute alcoholism, and preoperative apprehension and anxiety.

5 KLOPININ® (clonazepam) is 5-(2-chlorophenyl)-1,3-dihydro-7-nitro-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 2475). Klonopin is useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant), akinetic and myoclonic
10 seizures. Klonopin is also indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV.

TRANXENE® (clorazepate dipotassium) is indicated for the management of anxiety disorders or for the short-term relief
15 of the symptoms of anxiety, as adjunctive therapy in the management of partial seizures, and for the symptomatic relief of acute alcohol withdrawal (Physician's Desk Reference® 52 Edition 1998, pages 472-473).

20 VALIUM® (diazepam) is a benzodiazepine derivative. Chemically, diazepam is 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 2527). Valium is indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety.

25 PROSOM™ (estazolam tablets) is 8-chloro-6-phenyl-4H-s-triazolo[4-3- α][1,4]benzodiazepine (Physician's Desk Reference® 52 Edition 1998, pages 470-471). ProSom (estazolam) is indicated for the short-term management of insomnia characterized by difficulty in falling asleep,
30 frequent nocturnal awakenings, and/or early morning awakenings.

ROMAZICON® (flumazenil) is a benzodiazepine receptor antagonist (Physician's Desk Reference® 52 Edition 1998, pages 2494-2495). Chemically, flumazenil is ethyl 8-fluoro-
35 5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a](1,4)benzodiazepine-3-carboxylate. ROMAZICON is indicated

for the complete or partial reversal of the sedative effects of benzodiazepines in cases where general anesthesia has been induced and/or maintained with benzodiazepines, where
5 sedation has been produced with benzodiazepines for diagnostic and therapeutic procedures, and for the management of benzodiazepine overdose.

DALMANE® (flurazepam hydrochloride) is chemically 7-chloro-1-[2-(di-ethylamino)ethyl]-5-(o-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one dihydrochloride
10 (Physician's Desk Reference® 52 Edition 1998, page 2520). Dalmane is a hypnotic agent useful for the treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning
15 awakenings.

ATIVAN® (lorazepam) has the chemical formula, 7-chloro-5-(o-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 3013). Ativan (lorazepam) is indicated for the
20 management of anxiety disorders or for the short-term relief of the symptoms of anxiety or anxiety associated with depressive symptoms.

VERSED® (midazolam HCl) is 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine (Physician's
25 Desk Reference® 52 Edition 1998, pages 2512-2513).

SERAX® (oxazepam) is the first of a chemical series of compounds known as the 3-hydroxybenzodiazepinones (Physician's Desk Reference® 52 Edition 1998, page 3132). Serax (oxazepam) is indicated for the management of anxiety
30 disorders or for the short-term relief of the symptoms of anxiety.

DORAL® (quazepam) is a trifluoroethyl benzodiazepine hypnotic agent, having the chemical name 7-chloro-5-(o-fluoro-phenyl)-1,3-dihydro-1-(2,2,2-trifluoroethyl)2H-1,4-benzodiazepine-2-thione (Physician's Desk Reference® 52
35 Edition 1998, page 2958). DORAL is indicated for the treatment of insomnia characterized by difficulty in falling

asleep, frequent nocturnal awakenings, and/or early morning awakenings.

RESTORIL® (temazepam) is a benzodiazepine hypnotic agent. The chemical name is 7-chloro-1,3-dihydro-3-hydroxy-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (Physician's Desk Reference® 52 Edition 1998, page 1894). RESTORIL® (temazepam) is indicated for the short-term treatment of insomnia (generally 7-10 days).

HALCION® Tablets contain triazolam, a triazolozodiazepine hypnotic agent (Physician's Desk Reference® 52 Edition 1998, pages 2275-2276). HALCION is indicated for the short-term treatment of insomnia (generally 7-10 days).

Antipsychotic agents are used primarily in the management of patients with psychotic or other serious psychiatric illness marked by agitation and impaired reasoning. These drugs have other properties that possibly are useful clinically, including antiemetic and antihistamine effects and the ability to potentiate analgesics, sedatives, and general anesthetics. Antipsychotic agents can also be used with optically pure R(-) fluoxetine. Tricyclic antipsychotic drugs fall into three subtypes: phenothiazines, thioxanthenes and other heterocyclic compounds.

Examples of phenothiazines include, but are limited to: THORAZINE® (chlorpromazine), SERENTIL® (mesoridazine besylate), MELLARIL® or MILLAZINE® (thioridazine), TINDAL® (acetophenazine), PERMITIL® or PROLIXIN® (fluphenazine) TRILAFON® (perphenazine) and STELAZINE® (trifluoperazine) (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 18, p404, Table 18-1).

THORAZINE® (chlorpromazine) is 10-(3-dimethylaminopropyl)-2-chlorophenothiazine, a dimethylamine derivative of phenothiazine (Physician's Desk Reference® 52 Edition 1998, pages 2870-2871). THORAZINE® (chlorpromazine)

is indicated, *inter alia*, for the management of manifestations of psychotic disorders.

SERENTIL® (mesoridazine besylate) is 10-[2(1-methyl-2-piperidyl)ethyl]-2-methyl-sylfinyl)-phenothiazine (Physician's Desk Reference® 52 Edition 1998, pages 725-726). Serentil® (mesoridazine besylate) is indicated in the treatment of, *inter alia*, emotional withdrawal, conceptual disorganization, anxiety, tension, hallucinatory behavior, suspiciousness and blunted affect in schizophrenic patients.

TRILAFON® (perphenazine) is (4-[3-(2-chlorophenothiazin-10-yl)propyl-1-piperazineethanol) (Physician's Desk Reference® 52 Edition 1998, page 2666). TRILAFON® (perphenazine) is indicated for use in the management of the manifestations of psychotic disorders and for the control of severe nausea and vomiting in adults.

STELAZINE® (trifluoperazine) is indicated for the management of the manifestations of psychotic disorders and for the short-term treatment of generalized non-psychotic anxiety (Physician's Desk Reference® 52 Edition 1998, page 2862).

Examples of thioxanthenes include, but are limited to: TARACTAN® (chlorprothixene) and NAVANE® (thiothixene) (Goodman & Gilman, The Pharmacological Basis of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 18, p404, Table 18-1).

NAVANE® (thiothixene) is the *cis* isomer of N,N-dimethyl-9-[3-(4-methyl-1-piperazinyl)-propylidene]thioxanthene-2-sulfonamide (Physician's Desk Reference® 52 Edition 1998, page 2192). NAVANE® (thiothixene) is indicated in the management of manifestations of psychotic disorders.

Examples of the other heterocyclic compounds that can be used in combination with R(-) fluoxetine include, but are limited to: CLOZARIL® (clozapine), HALDOL® (haloperidol), LOXITANE® (loxapine), MOBAN® (molindone), ORAP® (Pimozide), RISPERDAL® (risperidone) and NORPRAMIN® (desipramine hydrochloride) (Goodman & Gilman, The Pharmacological Basis

of Therapeutics, 9th Ed. McGraw-Hill, 1996, Chapter 18, p404, Table 18-1).

5 CLOZARIL® (clozapine) is a tricyclic dibenzodiazepine derivative, 8-chloro-11-(4-methyl-1-piperazinyl)5H-dibenzo[b,e][1,4]diazepine (Physician's Desk Reference® 52 Edition 1998, page 1834). CLOZARIL® (clozapine) is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment.

10 HALDOL® (haloperidol) is 4-[4-(p-chlorophenyl)-4-hydroxy-piperidonol-4'-fluorobutyrophenone (Physician's Desk Reference® 52 Edition 1998, pages 1997-1998). HALDOL® (haloperidol) is indicated, *inter alia*, for use in the management of manifestations of psychotic disorders, for the control of tics and vocal utterances of Tourette's Disorder in children and adults, for the treatment of severe behavior problems in children of combative.

15 LOXITANE® (loxapine) is 2-Chloro-11-(4-methyl-1-piperazinyl)dibenz[b,f][1,4]oxaxepine (Physician's Desk Reference® 52 Edition 1998, page 1396). LOXITANE® (loxapine) is indicated for the management of the manifestations of psychotic disorders.

20 MOBAN® (molindone) is 3-ethyl-6,7-dihydro-2-methyl-5-(morpholinomethyl) indol-4(5H)-one hydrochloride (Physician's Desk Reference® 52 Edition 1998, pages 976-977). MOBAN® (molindone) is indicated for the management of the manifestations of psychotic disorders.

25 ORAP® (Pimozide) is 1-[1-[4,4-bis(4-fluorophenyl)butyl]4-piperidinyl]-1,3-dihydro-2H-benzimidazole-2-one (Physician's Desk Reference® 52 Edition 1998, page 978). ORAP® (Pimozide) is indicated for the suppression of motor and phonic tics in patients with Tarried's Disorder who have failed to respond satisfactorily to standard treatment.

35 RISPERDAL® (risperidone) is 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-

methyl-4H-pyrido[1,2-a]pyrimidin-4-one (Physician's Desk Reference® 52 Edition 1998, pages 130-131). RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

NORPRAMIN® (desipramine hydrochloride) is 5H-Dibenz[bf]azepine-5-propanamine, 10, 11- dihydro-N-methyl-, monohydrochloride (Physician's Desk Reference® 52 Edition 1998, page 1227). NORPRAMIN® (desipramine hydrochloride) is indicated for the treatment of depression.

Examples of 5-HT_{1A} receptor antagonists and/or β -adrenergic antagonists that can be used with R(-) fluoxetine in accordance with this invention include, but are limited to, alprenolol, WAY 100135, spiperone, VISKEN™ (pindolol), (S)-UH-301, LEVATOL™ (penbutolol), INDERAL™ (propranolol) and tertatolol.

Alprenolol (1-(1-methylethyl)amino-3-[2-(2-propenyl)phenoxy]-2-propanol) was disclosed by Brandstrom et al., U.S. Patent 3,466,325, which shows its preparation.

WAY 100135 (N-(t-butyl)-3-[4-(2-methoxyphenyl)piperazin-1-yl]-2-phenylpropanamide) was disclosed by Abou-Gharbia et al., U.S. Patent 4,988,814, which disclosed that the compound has affinity for the 5-HT_{1A} receptor. Cliffe et al., *J. Med. Chem.*, 36:1509-10 (1993) showed that the compound is a 5-HT_{1A} antagonist.

Spiperone (8-[4-(4-fluorophenyl)-4-oxobutyl]-1-phenyl-1,3,8-triazaspiro[4,5]decan-4-one) is a well-known compound, taught in U.S. Patents 3,155,669 and 3,155,670. Its activity as a 5-HT_{1A} antagonist is shown by Middlmiss et al., *Neurosci. and Biobehav. Rev.*, 16:75-82, (1992).

Pindolol (4-(2-hydroxy-3-isopropylaminopropoxy)-indole) was disclosed by Troxler et al., U.S. Patent 3,471,515, which describes this compound as well as a beta-blocker. Dreshfield et al., *Neurochem. Res.*, 21(5):557-562 (1996) disclosed that S(-) pindolol is a 5-HT_{1A} antagonist. VISKEN™ (pindolol) is indicated in the management of hypertension (Physician's Desk Reference® 51 Edition 1997, page 2429). As

used in the present application, the term "pindolol" refers to any acid addition salt or the free base, and includes either the racemic mixture or either of the R and S enantiomers.

5 (S)-UH-301 ((S)-5-fluoro-8-hydroxy-2-dipropylamino-tetralin) is well known to pharmacologists and pharmaceutical chemists. Hillyer et al. taught its synthesis in *J. Med. Chem.*, 33:1541-44 (1990) and Moreau et al., *Brain Res. Bull.*, 29:901-04 (1992) provided considerable in vivo data about the
10 compound.

Penbutolol (1-(t-butylamino)-2-hydroxy-3-(2-cyclopentylphenoxy)propane) was taught by Ruschig et al., U.S. Patent 3,551,493, which describes it as a beta-blocker. Both the
15 (-) and the (+) enantiomers of penbutolol are of interest; the (-) enantiomer is preferred for the present purpose but both enantiomers and the racemic mixture are included in the word "penbutolol" in this document. LEVATOL™ (penbutolol) is indicated in the management of hypertension (Physician's Desk
20 Reference® 51 Edition 1997, page 2547).

Propranolol (1-isopropylamino-3-(1-naphthalenyloxy)-2-propanol) was disclosed by Crowther et al., U.S. Patent 3,337,628 to be a beta-blocker like tertatolol. INDERAL™ (propranolol) is indicated in the management of hypertension.
25 INDERAL™ (propranolol) is also indicated in the management of myocardial infarction, migraine, essential tremor, hypertrophic subaortic stenosis and pheochromocytoma (Physician's Desk Reference® 51 Edition 1997, pages 2833-2834).

30 Tertatolol (8-(3-t-butylamino-2-hydroxypropyloxy)-thiochroman) was disclosed by Malen et al., U.S. Patent 3,960,891, which teaches it to be a blocker of cardiac beta-adrenergic receptors. Its other activities, including the presently used 5-HT_{1A} antagonist activity, have been
35 discovered since the original patents appeared.

Examples of non-benzodiazepine and non-tricyclic agents that can be used in this invention include, but are limited

to: ZYPREXA™ (olanzapine), BUSPAR® (buspirone hydrochloride), ATARAX® (hydroxyzine hydrochloride) and tomoxetine.

5 ZYPREXA™ (olanzapine) is 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine (Physician's Desk Reference® 52 Edition 1998, page 1512). ZYPREXA™ (olanzapine) is indicated for the management of the manifestations of psychotic disorders.

10 BUSPAR® (buspirone hydrochloride) is an anti-anxiety agent that is not chemically or pharmacologically related to the benzodiazepines, barbiturates, or other sedative/anxiolytic drugs (Physician's Desk Reference® 52 Edition 1998, page 782). Chemically, buspirone hydrochloride is 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-
15 azaspiro[4,5]decane-7,9-dione monohydrochloride. BUSPAR® (buspirone hydrochloride) is indicated for the treatment of Generalized Anxiety Disorder (ADA).

20 ATARAX® (hydroxyzine hydrochloride) is designated chemically as 1-(p-chlorobenzhydryl)-4[2-(2-hydroxyethoxy)-ethyl] piperazine dihydrochloride (Physician's Desk Reference® 52 Edition 1998, page 2164). ATARAX® (hydroxyzine hydrochloride) is indicated for symptomatic relief of anxiety and tension associated with psychoneurosis, as an adjunct in organic disease states in which anxiety is manifested, in the
25 management of pruritus due to allergic conditions, and as sedative when used as premedication and following general anesthesia.

30 While all combinations of R(-) fluoxetine and one or more above described biologically active compounds are useful and valuable, certain combinations are particularly valued and are preferred, as follows:

35 R(-) fluoxetine/alprazolam
R(-) fluoxetine/brotizolam
R(-) fluoxetine/chlordiazepoxide
R(-) fluoxetine/clobazam
R(-) fluoxetine/clonazepam
R(-) fluoxetine/clorazepate

	R(-) fluoxetine/demoxepam
	R(-) fluoxetine/diazepam
	R(-) fluoxetine/estazolam
5	R(-) fluoxetine/flumazenil
	R(-) fluoxetine/flurazepam
	R(-) fluoxetine/halazepam
	R(-) fluoxetine/lorazepam
	R(-) fluoxetine/midazolam
10	R(-) fluoxetine/nitrazepam
	R(-) fluoxetine/nordazepam
	R(-) fluoxetine/oxazepam
	R(-) fluoxetine/prazepam
	R(-) fluoxetine/quazepam
15	R(-) fluoxetine/temazepam
	R(-) fluoxetine/triazolam
	R(-) fluoxetine/chlorpromazine
	R(-) fluoxetine/mesoridazine
	R(-) fluoxetine/thioridazine
20	R(-) fluoxetine/acetophenazine
	R(-) fluoxetine/fluphenazine
	R(-) fluoxetine/perphenazine
	R(-) fluoxetine/trifluoperazine
	R(-) fluoxetine/chlorprothixene
25	R(-) fluoxetine/thiothixene
	R(-) fluoxetine/clozapine
	R(-) fluoxetine/haloperidol
	R(-) fluoxetine/loxapine
	R(-) fluoxetine/molindone
30	R(-) fluoxetine/pimozide
	R(-) fluoxetine/risperidone
	R(-) fluoxetine/alprenolol
	R(-) fluoxetine/WAY 100135
	R(-) fluoxetine/spiperone
35	R(-) fluoxetine/S(-) pindolol
	R(-) fluoxetine/R(+) pindolol
	R(-) fluoxetine/racemic pindolol

5 R(-) fluoxetine/(S)-UH-301
R(-) fluoxetine/penbutolol
R(-) fluoxetine/propranolol
R(-) fluoxetine/tertatolol
R(-) fluoxetine/desipramine
R(-) fluoxetine/clonidine
R(-) fluoxetine/olanzapine
R(-) fluoxetine/methylphenidate
10 R(-) fluoxetine/buspirone
R(-) fluoxetine/hydroxyzine
R(-) fluoxetine/tomoxetine

The magnitude of a prophylactic or therapeutic dose of R(-) fluoxetine, of course, vary with the nature of the severity of the condition to be treated and its route of administration. It will also vary according to the age, weight and response of the individual patient. In general the daily dose range of R(-) fluoxetine in treatment of diseases or disorders, especially psychotic or psychiatric diseases or disorders lie within the range from about 1 mg to about 100 mg per day, preferably about 5 mg to about 60 mg per day, and most preferably from about 10 mg to about 40 mg per day, in single or divided doses. Effective amounts of the therapeutic agents to be used in combination with R(-) fluoxetine are based on the recommended doses known to those skilled in the art for the various diseases or disorders. It should be noted that the attending physician would know how to and when to terminate, interrupt, or adjust therapy to lower dosage due to toxicity, bone marrow, liver or kidney dysfunctions or adverse drug-drug interaction. Conversely, the attending physician would also know to adjust treatment to higher levels if the clinical response is not adequate (precluding toxicity).

A therapeutically effective dose refers to that amount of the compound sufficient to result in amelioration of symptoms or a prolongation of survival in a patient. Toxicity and therapeutic efficacy of such compounds can be

determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD50 (the dose lethal to 50% of the population) and the ED50 (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD50/ED50. Compounds which exhibit large therapeutic indices are preferred. The data obtained from these cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED50 with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized. For any compound used in the method of the invention, the therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC50 *i.e.*, the concentration of the test compound which achieves a half-maximal inhibition of its target from infected cells compared to untreated control as determined in cell culture. Such information can be used to more accurately determine useful doses in humans.

In a certain embodiment of the invention, that is, a method of treating or preventing a psychotic or psychiatric disease or disorder, such as depression, an effective amount of R(-) fluoxetine and an effective amount of a biologically active 5-HT_{1A} receptor antagonist is administered for a first period of time; and then an effective amount of R(-) fluoxetine and a reduced amount of said biologically active 5-HT_{1A} receptor antagonist is administered for a second period of time. Preferably, 5-HT_{1A} receptor antagonist used herein is pindolol. Also preferably, the first period of time is from about 2 to about 6 weeks and the second period of time is from about 2 to about 20 days. A kit which comprises a

plurality of dosage forms each comprising an effective amount of R(-) fluoxetine, a plurality of dosage forms each comprising an effective amount of a biologically active 5-HT_{1A} receptor antagonist, and a plurality of dosage forms each comprising a reduced amount of said biologically active 5-HT_{1A} receptor antagonist can be used in the above method. A kit which comprises a single unit dosage form of an effective amount of R(-) fluoxetine, a single unit dosage form of an effective amount of a biologically active 5-HT_{1A} receptor antagonist, and a single unit dosage form of a reduced amount of said biologically active 5-HT_{1A} receptor antagonist can also be used in the above method.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the pharmaceutical compositions of the present invention. For example, oral, rectal, parenteral, transdermal, sublingual subcutaneous, intramuscular, inhalation and the like may be employed. Dosage forms include tablets, troches, dispersions, suspensions, solutions, capsules, patches and the like.

The pharmaceutical compositions of the present invention comprise R(-) fluoxetine and other active ingredients or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier and optionally other therapeutic ingredients. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids and organic acids.

Since R(-) fluoxetine, one of the key component of the pharmaceutical composition of the present invention, is basic, salts may be prepared from pharmaceutically acceptable nontoxic acids, including inorganic and organic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric,

pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric acid, p-toluenesulfonic and the like. Particularly preferred are hydrobromic, hydrochloric, phosphoric and sulfuric acids.

5 The compositions include compositions suitable for oral, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), although the most suitable route in any given case will depend on the nature and severity of the condition being treated. The most preferred route of the
10 present invention is oral. They may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

The pharmaceutical carrier, which is included in the pharmaceutical compositions of the present invention, may
15 take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example,
20 water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations, such as, for example, suspensions, elixir and solutions; or carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in
25 the case of oral solid preparations such as, for example, powders, capsules and tablets, with the solid oral preparations being preferred over the liquid preparations. The most preferred solid oral preparation is capsules. Because of their ease of administration, tablets and capsules
30 represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

35 In addition to the common dosage forms set out above, the pharmaceutical compositions of the present invention may also be administered by controlled release means and/or

delivery devices such as those described in U.S. Pat. Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; 3,630,200 and 4,008,719, the disclosures of which are hereby incorporated
5 by reference. The use of a racemic mixture of fluoxetine in a sustained release formulation is disclosed and/or claimed in U.S. Pat. Nos. 4,797,286 and 4,947,092.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete
10 units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be
15 prepared by any of the methods of pharmacy but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active
20 ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example, a tablet may be prepared by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be
25 prepared by compressing in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the
30 powdered compound moistened with an inert liquid diluent.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from
35 the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

Various references are cited herein, the disclosures of which are incorporated by reference in their entireties.

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What is claimed is:

1. A pharmaceutical composition which comprises
5 an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active benzodiazepine and a pharmaceutically acceptable carrier.
- 10 2. The pharmaceutical composition of claim 1, wherein said biologically active benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam,
15 halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam.
3. The pharmaceutical composition of claim 1, wherein the amount of R(-) fluoxetine is from about 5 mg to
20 about 100 mg.
4. The pharmaceutical composition of claim 1, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about
25 10,000:1.
5. The pharmaceutical composition of claim 1, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.
- 30 6. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active tricyclic antipsychotic compound and a pharmaceutically
35 acceptable carrier.

7. The pharmaceutical composition of claim 6,
wherein said biologically active tricyclic antipsychotic
compound is selected from the group consisting of
5 chlorpromazine, mesoridazine, thioridazine, acetophenazine,
fluphenazine, perphenazine, trifluoperazine, chlorprothixene,
thiothixene, clozapine, haloperidol, loxapine, molindone,
pimozide, risperidone and desipramine.
- 10 8. The pharmaceutical composition of claim 6,
wherein the amount of the R(-) fluoxetine is from about 5 mg
to about 100 mg.
- 15 9. The pharmaceutical composition of claim 6,
wherein the R(-) fluoxetine is present in an amount on weight
basis, relative to S(+) fluoxetine, from about 100:1 to about
10,000:1.
- 20 10. The pharmaceutical composition of claim 6,
wherein the pharmaceutically acceptable salt of R(-)
fluoxetine is R(-) fluoxetine hydrochloride.
- 25 11. A pharmaceutical composition which comprises
an effective amount of R(-) fluoxetine or a pharmaceutically
acceptable salt thereof, substantially free of its S(+)
stereoisomer, an effective amount of a biologically active 5-
HT_{1A} receptor antagonist and a pharmaceutically acceptable
carrier.
- 30 12. The pharmaceutical composition of claim 11,
wherein said biologically active 5-HT_{1A} receptor antagonist is
selected from the group consisting of alprenolol, WAY 100135,
spiperone, pindolol, (S)-UH-301, penbutolol, propranolol and
tertatolol.
- 35

13. The pharmaceutical composition of claim 11, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

5

14. The pharmaceutical composition of claim 11, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

10

15. The pharmaceutical composition of claim 11, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

15

16. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active compound selected from the group consisting of lorazepam, tomoxetine, olanzapine, respiradone, buspirone, hydroxyzine and valium and a pharmaceutically acceptable carrier.

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17. The pharmaceutical composition of claim 16, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

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18. The pharmaceutical composition of claim 16, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

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19. The pharmaceutical composition of claim 16, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

35

20. A pharmaceutical composition which comprises an effective amount of R(-) fluoxetine or a pharmaceutically

acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active compound selected from the group consisting of racemic pindolol, S(-) pindolol and R(+) pindolol and a
5 pharmaceutically acceptable carrier.

21. The pharmaceutical composition of claim 20,
wherein the amount of R(-) fluoxetine is from about 5 mg to
10 about 100 mg.

22. The pharmaceutical composition of claim 20,
wherein the R(-) fluoxetine is present in an amount on weight
basis, relative to S(+) fluoxetine, from about 100:1 to about
15 10,000:1.

23. The pharmaceutical composition of claim 20,
wherein the pharmaceutically acceptable salt of R(-)
fluoxetine is R(-) fluoxetine hydrochloride.

24. A pharmaceutical composition which comprises
an effective amount of R(-) fluoxetine or a pharmaceutically
acceptable salt thereof, substantially free of its S(+) stereoisomer, an effective amount of a biologically active 5-HT₁ receptor agonist, and a pharmaceutically acceptable
25 carrier.

25. The pharmaceutical composition of claim 24,
wherein the R(-) fluoxetine is present in an amount on weight
30 basis, relative to S(+) fluoxetine, from about 100:1 to about
10,000:1.

26. The pharmaceutical composition of claim 24,
wherein the pharmaceutically acceptable salt of R(-)
fluoxetine is R(-) fluoxetine hydrochloride.
35

27. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such
5 treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 1.

28. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which
10 comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 6.

29. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which
15 comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 11.

30. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which
20 comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 16.

31. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which
25 comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 20.
30

32. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which
35 comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of the pharmaceutical composition of claim 24.

33. A method of treating or preventing a disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer, and an effective amount of a biologically active benzodiazepine.

34. The method of claim 33, wherein the psychotic or psychiatric disease or disorder is depression.

35. The method of claim 33, wherein said biologically active benzodiazepine is selected from the group consisting of alprazolam, brotizolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, demoxepam, diazepam, estazolam, flumazenil, flurazepam, halazepam, lorazepam, midazolam, nitrazepam, nordazepam, oxazepam, prazepam, quazepam, temazepam and triazolam.

36. The method of claim 33, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

37. The method of claim 33, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

38. The method of claim 33, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

39. The method of claim 33, wherein said disease or disorder is a psychotic or psychiatric disease or disorder.

40. The method of claim 39, wherein the disease or disorder is selected from the group consisting of anxiety

disorder, depression, alcohol withdrawal, preoperative apprehension, Lennox-Gastaut syndrome (petit mal variant), seizures, panic disorder, skeletal muscle spasm, spasticity caused by upper motor neuron disorders, athetosis and stiffman syndrome, convulsive disorders and insomnia.

41. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a biologically active tricyclic antipsychotic compound.

42. The method of claim 41, wherein the psychotic or psychiatric disease or disorder is depression.

43. The method of claim 41, wherein said biologically active tricyclic antipsychotic compound is selected from the group consisting of chlorpromazine, mesoridazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, chlorprothixene, thiothixene, clozapine, haloperidol, loxapine, molindone, pimozide, risperidone and desipramine.

44. The method of claim 41, wherein the amount of the R(-) fluoxetine is from about 5 mg to about 100 mg.

45. The method of claim 41, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

46. The method of claim 41, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

47. The method of claim 43, wherein the disease or disorder is selected from the group consisting of anxiety disorder, depression, nausea, vomiting, restlessness and apprehension before surgery, acute intermittent porphyria, tetanus, intractable hiccups, severe behavioral problems and hyperactivity in children, emotional withdrawal, conceptual disorganization, tension, hallucinatory behavior, suspiciousness and blunted affect in schizophrenic patients and Tourette's Disorder.

48. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a 5-HT_{1A} receptor antagonist.

49. The method of claim 48, wherein the psychotic or psychiatric disease or disorder is depression.

50. The method of claim 48, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

51. The method of claim 48, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

52. The method of claim 48, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

53. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of

R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a 5-HT₂ receptor agonist.

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54. The method of claim 53, wherein the psychotic or psychiatric disease or disorder is depression.

55. The method of claim 53, wherein the amount of
10 R(-) fluoxetine is from about 5 mg to about 100 mg.

56. The method of claim 53, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

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57. The method of claim 53, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

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58. A method of treating or preventing post-myocardial infarction depression in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially
25 free of its S(+) stereoisomer, and an effective amount of a β -adrenergic antagonist.

59. The method of claim 58, wherein the β -adrenergic antagonist is S(-) pindolol.

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60. The method of claim 58, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

61. The method of claim 58, wherein the R(-) fluoxetine is present in an amount on weight basis, relative
35 to S(+) fluoxetine, from about 100:1 to about 10,000:1.

62. The method of claim 58, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

5
63. A method of treating or preventing posttraumatic stress disorder in a mammal which comprises administering to said mammal, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine,
10 or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a 5-HT_{1A} receptor antagonist.

64. The method of claim 63, wherein the 5-HT_{1A}
15 receptor antagonist is S(-) pindolol or R(+) pindolol.

65. The method of claim 63, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.

20 66. The method of claim 63, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.

67. The method of claim 63, wherein the
25 pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

68. A method of treating or preventing a psychotic or psychiatric disease or disorder in a mammal which
30 comprises:

a) administering to said mammal an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer, and an effective amount of a biologically
35 active 5-HT_{1A} receptor antagonist for a first period of time; and

- 5 b) after the first period of time, administering to said mammal an effective amount of R(-) fluoxetine or a pharmaceutically acceptable salt thereof substantially free of its S(+) stereoisomer and a reduced amount of said biologically active 5-HT_{1A} receptor antagonist for a second period of time.
- 10 69. The method of claim 68, wherein the psychotic or psychiatric disease or disorder is depression.
- 15 70. The method of claim 68, wherein the biologically active 5-HT_{1A} receptor antagonist is S(-) pindolol or R(+) pindolol.
71. The method of claim 68, wherein the amount of R(-) fluoxetine is from about 5 mg to about 100 mg.
- 20 72. The method of claim 68, wherein the R(-) fluoxetine is present in an amount on weight basis, relative to S(+) fluoxetine, from about 100:1 to about 10,000:1.
- 25 73. The method of claim 68, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.
74. The method of claim 68, wherein the first period of time is about 2 to 6 weeks.
- 30 75. The method of claim 68, wherein the second period of time is about 5 to 20 days.
- 35 76. A kit which comprises:
a) a plurality of dosage forms each comprising an effective amount of R(-) fluoxetine or a

pharmaceutically acceptable salt thereof
substantially free of its S(+) stereoisomer;

- 5 b) a plurality of dosage forms each comprising an effective amount of a biologically active 5-HT_{1A} receptor antagonist; and
- c) a plurality of dosage forms each comprising a reduced amount of said biologically active 5-HT_{1A} receptor antagonist.

10 77. The kit of claim 76, wherein the biologically active 5-HT_{1A} receptor antagonist is S(-) pindolol or R(+) pindolol.

15 78. The kit of claim 76, wherein the pharmaceutically acceptable salt of R(-) fluoxetine is R(-) fluoxetine hydrochloride.

20 79. A method of treating posttraumatic stress disorder in a human which comprises administering to said human, to which such treatment or prevention is needed, an effective amount of R(-) fluoxetine, or a pharmaceutically acceptable salt thereof, substantially free of its S(+) stereoisomer, and an effective amount of a biologically

25 active compound.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 45/06, A61P 25/18, 25/24, 25/22, 25/14 // (A61K 45/06, 31:135)	A3	(11) International Publication Number: WO 99/61014 (43) International Publication Date: 2 December 1999 (02.12.99)
(21) International Application Number: PCT/US99/11725 (22) International Filing Date: 27 May 1999 (27.05.99) (30) Priority Data: 09/086,262 28 May 1998 (28.05.98) US (71) Applicant: SEPRACOR INC. [US/US]; 111 Locke Drive, Marlborough, MA 01752 (US). (72) Inventors: BARBERICH, Timothy, J.; 73 Nashoba Road, Concord, MA 01742 (US). RUBIN, Paul, D.; 37 Greystone Lane, Sudbury, MA 01776 (US). HANDLEY, Dean, A.; 17 Garfield Drive, Westborough, MA 01581 (US). (74) Agents: LAWRENCE, Stanton, T. et al.; Pennie & Edmonds LLP, 1155 Avenue of the Americas, New York, NY 10036 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> (88) Date of publication of the international search report: 20 July 2000 (20.07.00)
(54) Title: COMPOSITIONS AND METHODS EMPLOYING R(-) FLUOXETINE AND OTHER ACTIVE INGREDIENTS (57) Abstract Pharmaceutical compositions which comprise R(-) fluoxetine and one or more other biologically active compounds are disclosed. Methods of treating or preventing a disease or disorder, especially a psychotic or psychiatric disease or disorder, using the above pharmaceutical composition or by administering a R(-) fluoxetine in combination with one or more other biologically active compounds are also disclosed. Methods of treating patients having or at risk of having AIDS or HIV infection, cancer, cardiac disorder, post-myocardial depression and post-traumatic stress disorder using optically pure R(-) fluoxetine in combination with one or more other biologically active compounds are further disclosed.		

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 99/11725

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K45/06 A61P25/18 A61P25/24 A61P25/22 A61P25/14
//(A61K45/06,31:135)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FULLER AND PERRY: "Comparison of Fluoxetine and Norfluoxetine Enantiomers as Inhibitors of Hexobarbitone in Mice" PHARMACY AND PHARMACOLOGY, vol. 44, no. 12, December 1992 (1992-12), pages 1041-4042, XP000889620 the whole document	1-79
X	US 5 747 494 A (BILLARDON MARTINE ET AL) 5 May 1998 (1998-05-05) the whole document	16-19,30

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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents

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L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search

12 April 2000

Date of mailing of the international search report

18.04.00

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11725

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EP 0 722 941 A (LILLY CO ELI) 24 July 1996 (1996-07-24)</p> <p>page 97, line 37-48 page 97, line 54 -page 98, line 1 page 99-100; claim 19</p>	<p>11, 13-15, 29, 48-52, 63, 65-69, 71-76,78</p>
X	<p>EP 0 687 472 A (LILLY CO ELI) 20 December 1995 (1995-12-20)</p> <p>page 2, line 28-32 page 6, line 3-29 page 7; claims 1,2,4,5,10,12-15 page 11, line 15-60 page 12, line 25-39 page 13, line 1-15 page 13, line 36 -page 14, line 36</p>	<p>11-15, 20-23, 29,31, 58-78</p>
X	<p>EP 0 759 299 A (LILLY CO ELI) 26 February 1997 (1997-02-26)</p> <p>page 5, line 45-52; claims 1,2</p>	<p>11-15, 29, 48-52, 58-63, 65-69, 71-76,78</p>
X	<p>VON MOLTKE ET AL: "Differential Inhibition of Desipramine Hydroxylation in vitro by the Enantiomers of Fluoxetine" CLINICAL PHARMACOLOGY AND THERAPEUTICS, vol. 57, no. 2, February 1995 (1995-02), page 205 XP000889632</p> <p>the whole document</p>	<p>6-15, 24-26, 28,29, 32, 41-57, 63, 65-69, 71-76,78</p>
Y	<p>EP 0 792 649 A (LILLY CO ELI) 3 September 1997 (1997-09-03)</p> <p>the whole document</p>	<p>11-15, 20-23, 29,31, 48-52, 59,65-78</p>

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11725

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 92 00103 A (BEECHAM GROUP PLC) 9 January 1992 (1992-01-09) the whole document ---	11-15, 24-26, 29,32, 53-57, 63, 65-69, 71-76,78
Y	WO 96 33710 A (ASTRA AB) 31 October 1996 (1996-10-31) the whole document ---	11, 13-15, 29, 48-52, 63, 65-69, 71-76,78
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A	WO 92 13452 A (SEPRACOR INC) 20 August 1992 (1992-08-20) ---	1,16-19, 27,33,79
A	ROBERTSON, DAVID W. ET AL: "The absolute configurations and pharmacological activities of the optical isomers of fluoxetine, a selective serotonin-uptake inhibitor" J. MED. CHEM. (1988), 31(7), 1412-17,1988, XP000568845 page 1413, left-hand column, paragraphs 2,3 --- -/--	1,6,11, 16-20, 24, 27-33, 41,48, 53,58, 63,68, 76,79

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/11725

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SCHMIDER, JURGEN (1) ET AL: "Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: Studies of phenytoin p-hydroxylation." BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, (NOV., 1997) VOL. 44, NO. 5, PP 495-498., XP002119300 page 497, right-hand column, paragraph 3 page 496, right-hand column, paragraph 1 ---	1-79
A	WO 95 28152 A (SEPRACOR INC) 26 October 1995 (1995-10-26) page 1-10; claims ---	1-79
A	ASPESLET, LAUNA J. ET AL: "The effects of desipramine and iprindole on levels of enantiomers of fluoxetine in rat brain and urine" CHIRALITY (1994), 6(2), 86-90,1994, XP002132065 the whole document ---	6-15, 24-26, 28,29, 32, 41-57, 63, 65-69, 71-76,78
A	US 4 940 585 A (HAPWORTH WILLIAM E ET AL) 10 July 1990 (1990-07-10) -----	1-79

INTERNATIONAL SEARCH REPORT

national application No.
PCT/US 99/11725

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although all claims are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5, 27, 33-40, 79; partly 16-19, 30

Methods and compositions of R(-) fluoxetine combined with a benzodiazepine, including olanzapine, lorazepam and diazepam (valium), used in therapeutic applications; treating posttraumatic stress disorder with R(-) fluoxetine combined with any other biologically active compound.

2. Claims: Partly 6-10, 28, 41-47

Methods and compositions of R(-) fluoxetine combined with a tricyclic antipsychotic compound, e.g. the compounds of claim 7, excluding haloperidol, molindone, pimozide and risperidone; used in therapeutic applications.

3. Claims: 48-52; partly 11-15, 12, 29, 63, 65-69, 71-76, 78

Methods and compositions of R(-) fluoxetine combined with a 5-HT_{1A} receptor antagonist; used in therapeutic applications.

4. Claims: 24-26, 32, 53-57

Methods and compositions of R(-) fluoxetine combined with a 5-HT₃ receptor antagonist; used in therapeutic applications.

5. Claims: Partly 58, 60-62

Methods of combining R(-) fluoxetine with a beta-adrenergic antagonist, for use in therapeutic applications.

6. Claims: Partly 6-10, 16-19, 28, 30, 41-47

Methods and compositions of R(-) fluoxetine combined with a non-tricyclic antipsychotic agent chosen from haloperidol, molindone, pimozide and risperidone; used in therapeutic applications.

7. Claims: Partly 16-19, 30

Methods and compositions of R(-) fluoxetine combined with tomoxetine; used in therapeutic applications.

8. Claims: Partly 16-19, 30

Methods and compositions of R(-) fluoxetine combined with

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

hydroxyzine; used in therapeutic applications.

9. Claims: 20-23, 31, 59, 64, 70, 77; partly 11-15, 29, 58,
60-63, 65-69, 71-76, 78

Methods and compositions of R(-) fluoxetine combined with
pindolol; used in therapeutic applications.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.2

Present claims 11, 24, 48, 53, 58, 63, 68, 76 and 79 relate to compositions and methods defined by reference to a desirable characteristic or property, namely to antagonism of the 5-HT_{1A} or 5-HT₃ receptor (claims 11, 24, 48, 53, 63, 68, 76), or beta-adrenergic antagonism (claim 58), or to being "biologically active" (claim 79). The claims cover all compositions and methods having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compositions and methods.

In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). The definition of a compound or composition by its mechanism of action and/or pharmacological profile, as it is done in the claims mentioned above and claim 6, makes a complete search virtually impossible. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Furthermore, the compounds of claims 1 and 6 relate to an extremely large number of possible compounds falling within the terms "benzodiazepine" and "tricyclic" antipsychotic*. In fact, the claims cover so many options that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

* Similar to the above (definition by reference to a desirable characteristic), the term "antipsychotic" in claim 6 is as such not clear. Besides, in the light of the description, page 7, lines 11-12 and page 5, line 36 - page 6, line 1, it is not clear whether only tricyclic antidepressants, or tricyclic antipsychotics, or only compounds that are both, are meant.

Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compositions and methods as defined for the second active beside R-fluoxetine in claims 2, 7, 12, 16, 20, 59, 64, 70 and 77; in the description, page 8, line 31 - page 9, line 11; page 12, line 14 - page 15, line 13; page 15, line 22 - page 22, line 11; and by means of searching the general principle underlying the application.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/11725

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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